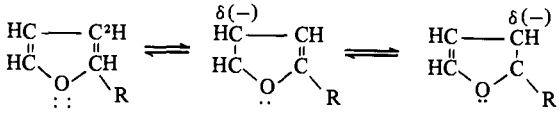
is correctly placed in the rotational diagram.[5] The interatomic distances are represented in Table I.

By applying the data to a series of similar pharmacologically active agents, two active sites are determined: the quaternary N and the -O- with the interatomic distances similar to corresponding centers of ACh, muscarone, and muscarine (2.8 ± 0.6 Å). The third active center in the FTA system may be demonstrated by noting only the order of charge distributions in EHT calculations. The EHT calculations reveal the largest negative charge, excluding the -O-, to be located on atoms C(1) and C(2). Likewise, the contributing resonance forms of the FTA structure II suggest a



II

negative charge to be situated at these same sites. It will be our purpose to correlate spatially this most negative carbon atom with the third center proposed by Kier.

An interatomic distance of 4.9-5.4 Å has been reported between the quaternary N and the C=O or the -OH of ACh, muscarone, and muscarine and 3.0 Å between the -O- and this third center in these systems.[3]

Similar active centers are reported in studies using conformationally restricted analogs of muscarinic agents—the dioxolanes. According to Garrison[7] and May,[8] 4.6 Å separate the N and one of the ether oxygens and 3.6 Å the N and the other -O- center. In further support of this hypothesis, Beckett[9] studied series of muscarine analogs using stereoselectivity in the reactions of cholinesterase and cholinergic receptors. He postulated distances of 4-7 Å and approximately 3 Å separating an anionic cavity and two positively charged points in the muscarinic receptor, corresponding to the quaternary N, the -O-, and C=O. Recently Baker, *et al.*,[10] described the conformation of the 3-methyl derivative of FTA using X-ray data. The distances separating the -O- and the quaternary N and C(1) and the quaternary N in this highly active muscarinic system are extremely close to those calculated of the unsubstituted compound using EHT. No attempt was made by these authors to designate C(1) as a third active center. It should be noted that a correlation here would yield evidence in favor of a three-centered muscarinic receptor.

Our molecular orbital results in Table I show good spatial correlation between centers N(7), O(4), and the most negative, ring carbon C(1) in FTA and the N, -O-, and C=O (-OH) of ACh, muscarine, and muscarone. Even better agreement is seen in the 1,3-dioxolane analogs and the 3-methyl-FTA derivative supporting both the concept of a three-centered muscarinic pharmacophore and the validity of describing biologically active agents *via* molecular orbital treatments. Our computational results suggest that a "three-centered receptor" is most important in the early stages of drug-receptor interaction.

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Silyl Ether Precursor-Type Insect Repellents[1]

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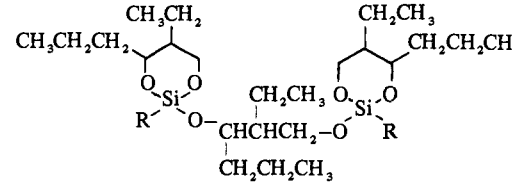
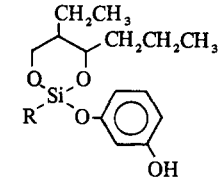
As an extension to our continued interest in the development of insect repellents with prolonged activity, we have synthesized compounds incorporating an insect-repellent component and one capable of anchoring to the skin. The novel entities, called "precursor molecules," may themselves be effective repellents; however, it is the gradual breakdown of the latter which is expected to provide perdurable repellency through sustained release of the repellent component. The rationale of this approach has previously been discussed in detail.[2,3] The reported[4] insectifugal activity of several heterocyclic silicon compounds **1**–**4** which incorporate the



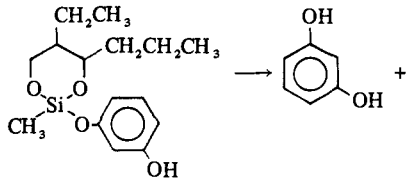
1, R = CH_3
2, R = $CH_3CH_2CH_2$
3, R = $CH_3CH_2CH_2CH_2CH_2$
4, R = C_6H_5

standard insect repellent 2-ethyl-1,3-hexanediol (Rutgers 612) in their structures prompted us to include this repellent into a precursor molecule through silyl ether linkages with resorcinol. Compounds **5**–**7** are designed to bind to the skin *via* the phenolic moiety and gradually release the repellent diol through hydrolysis of the silyl ether linkages subsequent to dermal application. There is considerable evidence to suggest that these silyl ethers would be readily

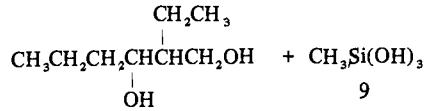


5, R = CH_3
6, R = CH_3CH_2
7, R = $CH_3CH_2CH_2CH_2$

susceptible to hydrolysis and that steric factors (*i.e.*, nature of the R group) play a predominant role in the rates of hydrolysis.[5a,6-8] Therefore, by varying the size of the R group, the rate of cleavage could conceivably be controlled to afford the optimal release of repellent diol **8**. Due to the tendency of silanetriols to undergo polymerization,[5b,6,7] **9** (and also the corresponding silanetriols of **6** and **7**) should



5

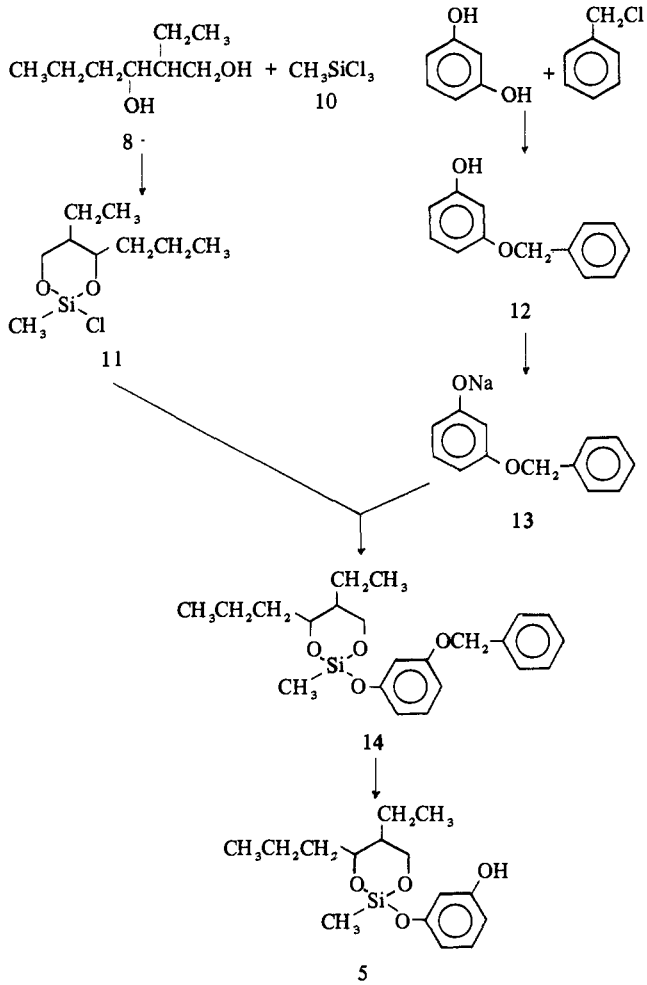


8 9

be quickly converted to a polysiloxane, a class of compounds noted for their lack of physiological activity and inert character.[9] An exhaustive search of the literature[10] did not reveal any findings which would suggest an alkylsilanetriol, or its condensation products, to be toxic.

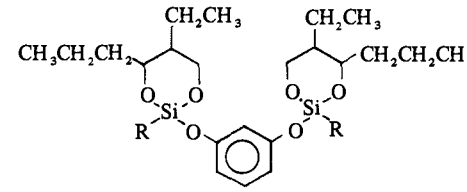
The synthetic pathway in Scheme I for the methyl analogs

Scheme I



illustrates the method employed in the preparation of the title compounds. Compound 12 was prepared by the method of Fitton and Ramage,[11] who report that rearrangement of 12 to 4-benzylresorcinol occurs when mineral acid is used in the isolation of the product. It was found in our laboratories that this rearrangement also occurred under thermal conditions.

Upon attempted purification of compounds 5-7 by distillation *in vacuo*, the corresponding bis compounds 15-17 were obtained as evidenced by spectral data (mass, nmr, ir, and uv). These compounds are probably formed under thermal conditions by an intermolecular reaction eliminating resorcinol. While 5 was converted almost quantitatively to 15, the more sterically hindered 7 afforded only small quantities of 17, thus illustrating the steric effects of Si-alkyl groups.



15, R = CH_3
16, R = CH_3CH_2
17, R = $CH_3CH_2CH_2CH_2$

Preparative thin-layer chromatography was attempted for the purification of 7 (theoretically the most stable); however hydrolysis occurred even under stringent anhydrous conditions. Catalytic hydrogenation of pure samples of 14, 18, and 19 afforded compounds 5-7 which are initially homogenous as evidenced by spectral characteristics. There is evidence that compounds 5-7, especially 5, are converted to 15-17, respectively, upon standing at ambient temperatures.

Experimental Section†

2-Chloro-5-ethyl-2-methyl-4-propyl-2-siladioxane-1,3 (11). To a cooled (−2 to 0°) solution of 204.5 g (1.368 mol) of freshly distilled CH_3SiCl_3 in 600 ml of anhydrous Et_2O was added dropwise a solution of 100 g (0.684 mol) of distilled 8‡ in 108.2 g (1.368 mol) of dry pyridine and 200 ml of anhydrous Et_2O. After standing for 1 hr (−2 to 0°), the pyridine hydrochloride was removed by filtration and the filtrate was distilled *in vacuo* affording a clear colorless liquid residue which was dried *in vacuo* and then distilled, 11 being obtained in 59.3% yield (90.4 g): bp 82.0–82.8° (3.2–4.0 mm); $n^{25}D$ 1.4387. *Anal.* ($C_9H_{19}ClO_2Si$) C, H, Cl, Si.

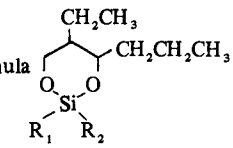
2-(3-Benzyloxyphenoxy)-5-ethyl-2-methyl-4-propyl-2-siladioxane-1,3 (14). To a cooled (−5°) solution of 29.5 g (0.133 mol) of 13 in 150 ml of anhydrous Et_2O was added dropwise 30.7 g (0.138 mol) of 11 in 100 ml of dry Et_2O. The reaction mixture was allowed to stir at 0° for 1 hr and then at ambient temperature for 4 days. The reaction mixture was filtered and the solvent removed *in vacuo* affording a brown residual oil which was distilled *in vacuo*, 14 being obtained in 36.4% yield (18.7 g): bp 182–184° (0.08 mm); $n^{25}D$ 1.5157; $\nu_{max}^{CCl_4}$ 1260 (COC) and 960–1180 cm^{-1} (SiOC); λ_{max}^{EtOH} 209 mμ (ε 18,640), 275 (2160), and 281 (1850); nmr ($CDCl_3$) δ 7.3 (m, 6), 6.5 (m, 3), 5.01 (s, 2, OCH_2), 3.9 (m, 3, $SiOCH_2$, SiOCH), 1.2 (m, 13), and 0.2 ppm (m, 3, CH_3Si). *Anal.* ($C_{22}H_{30}O_4Si$) C, H; Si: calcd, 7.27; found, 8.30, 8.38.

5-Ethyl-2-(3-hydroxyphenoxy)-2-methyl-4-propyl-2-siladioxane-1,3 (5). 5 was prepared by the hydrogenation of 14 using a Brown hydrogenator in which H_2 was generated by adding $NaBH_4$ in absolute EtOH to P_2O_5 in dry dioxane. A sample of 5.76 g (0.0149 mol) of 14 in 25 ml of anhydrous dioxane with 501.9 mg of 10% Pd/C

†Boiling points are uncorrected. Spectra (uv, ir, and nmr) were obtained with the Perkin-Elmer Model 202, the Beckman Model IR-33, and the Hitachi Perkin-Elmer Model R-24 spectrophotometers, respectively. Mass spectral analyses were carried out by the Morgan-Schaffer Corp., Montreal, Canada. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

‡Commercially available 2-ethyl-1,3-hexanediol (8), which is prepared by a base-catalyzed condensation of butyraldehyde and subsequent ester hydrolysis,[12] is a mixture of erythro and threo diastereoisomers. These isomers have been separated and characterized by Beroza and his coworkers[13] and found to have identical insect repellent characteristics. Compound 8 reported in this communication is a commercial mixture of isomers.

Table 1. Compounds of Formula



No.	R_1	R_2	Formula	Yield, %	Bp (mm), °C[a]	Analyses
11	CH_3	Chloro	$C_9H_{19}ClO_2Si$	59.3	82.0–82.8 (3.2–4.0)	C, H, Cl, Si
14	CH_3	3-Benzyloxyphenoxy	$C_{22}H_{30}O_4Si$	36.4	182–184 (0.08)	C, H, Si[b]
5	CH_3	3-Hydroxyphenoxy	$C_{15}H_{24}O_4Si$	84		C, H,[b] Si
20	CH_3CH_2	Chloro	$C_{10}H_{21}ClO_2Si$	45	57.0 (0.15)	C,[b] H, Cl,[b] Si[b]
18	CH_3CH_2	3-Benzyloxyphenoxy	$C_{23}H_{32}O_4Si$	32.5	178 (0.02)	C,[b] H, Si[b]
6	CH_3CH_2	3-Hydroxyphenoxy	$C_{16}H_{26}O_4Si$	97		C,[b] H, Si
21	$CH_3CH_2CH_2CH_2$	Chloro	$C_{12}H_{25}ClO_2Si$	70.4	76.9–79.5 (0.15–0.2)	C, H, Cl, Si
19	$CH_3CH_2CH_2CH_2$	3-Benzyloxyphenoxy	$C_{25}H_{36}O_4Si$	14	178–180 (0.01)	C,[b] H, Si[b]
7	$CH_3CH_2CH_2CH_2$	3-Hydroxyphenoxy	$C_{18}H_{30}O_4Si$	7.7[c]	133–137.5 (0.01)	C, H, Si[b]

[a] Boiling points are uncorrected. [b] 14, Si: calcd, 7.27; found, 8.30, 8.38. 5, H: calcd, 8.16; found, 8.68, 8.71. 20, C: calcd, 50.72; found, 51.74, 51.66. Cl: calcd, 14.97; found, 14.18, 14.16. Si: calcd, 11.86; found, 10.81, 10.79. 18, C: calcd, 68.96; found, 67.65, 67.58. Si: calcd, 7.01; found, 7.80, 7.73. 6, C: calcd, 61.90; found, 60.33, 60.30. 19, C: calcd, 70.05; found, 69.09, 69.25. Si: calcd, 6.55; found, 7.56, 7.46. 7, Si: calcd, 8.30; found, 9.77, 9.81. [c] In subsequent reactions in which the product was not purified by distillation, yields in excess of 85% were obtained; spectral evidence indicated the material was equivalent to the analytical sample.

was reduced; the glass tube connecting the two flasks was filled with molecular seive 4A to prevent H_2O and EtOH from entering the hydrogenation flask. The reaction mixture was filtered through Celite and the solvent removed by distillation *in vacuo* affording 3.7 g (84%) of **5** as pale yellow oil: n^{25}D 1.4942; $\nu_{max}^{CCl_4}$ 3600 cm^{-1} (OH); λ_{max}^{EtOH} 204 mμ (ε 8760) and 273 (1640); nmr ($CDCl_3$) δ 7.1 (m, 1, aromatic), 6.5 (m, 4, aromatic and OH), 3.9 (m, 3, OCH_2, OCH), 1.2 (m, 13), and 0.2 ppm (m, 3, $SiCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 253 (100), 169 (47), 153 (44), 135 (45), 110 (72), 69 (99). *Anal.* ($C_{15}H_{24}O_4Si$) C, Si; H: calcd, 8.16; found, 8.68, 8.71.

2-Chloro-2,5-diethyl-4-propyl-2-siladioxane-1,3 (20). Compound 20 was prepared in an analogous manner to that of 11, using 223.7 g (1.368 mol) of $CH_3CH_2SiCl_3$, 100.0 g (0.6838 mol) of 8, and 108.2 g (1.368 mol) of C_5H_5N. The crude product was purified by distillation *in vacuo*, the title compound being obtained in 45.0% yield (72.9 g): bp 57.0° (0.15 mm); n^{25}D 1.4428; $\nu_{max}^{CCl_4}$ (no OH); nmr ($CDCl_3$) δ 4.1 (m, 3, OCH_2 and OCH), and 1.2 ppm (m, 18). *Anal.* ($C_{10}H_{21}ClO_2Si$) H. Calcd: C, 50.72; Cl, 14.97; Si, 11.86. Found: C, 51.74, 51.66; Cl, 14.18, 14.16; Si, 10.81, 10.79.

2-(3-Benzyloxyphenoxy)-2,5-diethyl-4-propyl-2-siladioxane-1,3 (18). Similar to the preparation of 14, 18 was obtained from 46.9 g (0.211 mol) of **13**, 50.0 g (0.211 mol) of 20, and 300 ml of anhydrous Et_2O. The crude product was distilled *in vacuo* affording 18 in 32.5% yield (27.5 g): bp 178° (0.02 mm); n^{25}D 1.5147; $\nu_{max}^{CCl_4}$ 1260 (COC) and 1180–1050 cm^{-1} (SiOC); λ_{max}^{EtOH} 207 mμ (ε 17,920), 272 (1800), and 278 (1600); nmr ($CDCl_3$) δ 7.2 (m, 6, aromatic), 6.6 (m, 3, aromatic), 5.02 (s, 2, OCH_2), 3.9 (m, 3, $SiOCH_2$ and SiOCH), and 1.1 ppm (m, 18); mass spectrum (70 eV) *m/e* (rel intensity) 400 (40), 357 (20), 290 (11), 289 (8), 273 (9), 272 (9), 183 (8), 111 (12), 92 (37), 91 (100). *Anal.* ($C_{23}H_{32}O_4Si$) H. Calcd: C, 68.96; Si, 7.01. Found: C, 67.65, 67.58; Si, 7.80, 7.73.

2,5-Diethyl-2-(3-hydroxyphenoxy)-4-propyl-2-siladioxane-1,3 (6). Analogous to the synthesis of **5**, 6 was prepared from 12.06 g (0.03010 mol) of 18, 540.0 mg of 10% Pd/C, and 125 ml of anhydrous dioxane affording 9.1 g (97%) of 6 (a yellow oil): n^{25}D 1.4930; $\nu_{max}^{CCl_4}$ 3610 and 3360 cm^{-1} (OH); λ_{max}^{EtOH} 205 mμ (ε 10,970) and 275 (1600); nmr ($CDCl_3$) δ 7.1 (m, 1, aromatic), 6.5 (m, 4, aromatic and OH), 4.1 (m, 3, OCH_2 and OCH), 1.2 ppm (m, 18); mass spectrum (70 eV) *m/e* (rel intensity) 310 (34), 267 (100), 211 (20), 183 (46), 111 (39), 110 (54), 69 (75), 55 (56). *Anal.* ($C_{16}H_{26}O_4Si$) H, Si. Calcd: C, 61.90. Found: C, 60.33, 60.30.

2-Butyl-2-chloro-5-ethyl-4-propyl-2-siladioxane-1,3 (21). Compound 21 was prepared analogously to that of 11, using 50.0 g (0.342 mol) of distilled 8, 131.1 g (0.6843 mol) of freshly distilled n-$C_4H_9SiCl_3$, and 54.1 g (0.684 mol) of dry C_5H_5N. The crude product was distilled *in vacuo*, compound 21 being obtained in 70.4% yield (63.8 g): bp 76.9–79.5° (0.15–0.2 mm); n^{25}D 1.4460. *Anal.* ($C_{12}H_{25}ClO_2Si$) C, H, Cl, Si.

2-(3-Benzyloxyphenoxy)-2-butyl-5-ethyl-4-propyl-2-siladioxane-1,3 (19). Compound 19 was prepared in an analogous manner to that of 14, using 22.2 g (0.100 mol) of 13, 26.5 g (0.100 mol) of 21, and 250 ml of anhydrous Et_2O. The crude product was purified by distillation *in vacuo* employing a short-path, micro-distillation apparatus, affording 6.1 g (14%) of 19: bp 178–180° (0.01 mm); $\nu_{max}^{CCl_4}$ 1262 cm^{-1} (COC); λ_{max}^{EtOH} 207 mμ (ε 18,700), 273 (1890), and 279 (1660); mass spectrum (70 eV) *m/e* (rel intensity) 428 (58), 385 (25), 318 (15), 300 (11), 111 (11), 91 (100); isotope distribution calculated for $C_{25}H_{36}SiO_4$ *m/e* (rel intensity) 428 (100), 429 (32.9), 430 (9.2), found 428 (100), 429 (32.7), 430 (9.3). *Anal.* ($C_{25}H_{36}O_4Si$) H. Calcd: C, 70.05; Si, 6.55. Found: C, 69.09, 69.25; Si, 7.56, 7.46.

2-Butyl-5-ethyl-2-(3-hydroxyphenoxy)-4-propyl-2-siladioxane-1,3 (7). Analogous to compound **5**, 4.93 g (0.0115 mol) of 19, 517.5 mg of 10% Pd/C, and 125 ml of dry dioxane afforded a pale yellow, oily residue which was purified by distillation *in vacuo* employing a short-path apparatus, affording 0.3 g (7.7%) of 7: bp 133.0–137.5° (0.01 mm); $\nu_{max}^{CCl_4}$ 3600 and 3315 cm^{-1} (OH); mass spectrum (70 eV) *m/e* (rel intensity) 338 (22), 295 (65), 239 (20), 211 (14), 69 (100). *Anal.* ($C_{18}H_{30}O_4Si$) C, H; Si: calcd, 8.30; found, 9.77, 9.81. In subsequent reactions in which the product was not purified by distillation, yields in excess of 85% were obtained; spectral evidence indicated the material was equivalent to the analytical sample.

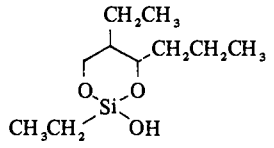
2,5-Diethyl-2-hydroxy-4-propyl-2-siladioxane-1,3 (22). In the purification of 18 by distillation *in vacuo*, the silanol was obtained in 4.6% yield (2.1 g): bp 120–138° (0.05–0.02 mm); $\nu_{max}^{CCl_4}$ 3340 (OH) and 1150–1000 cm^{-1} (SiOC); nmr ($CDCl_3$) δ 4.79 (s, 1, OH), 3.8 (m, 3, OCH_2 and OCH), and 1.1 ppm (m, 18).

Results and Discussion

Compounds **5–7** were tested for insect repellent activity against *Aedes aegypti* L. mosquitoes subsequent to application on the forearms of human volunteers; experimental details have been previously described (test C).[14] In comparing the insectifugal activity of these agents with the standard repellent, 2-ethyl-1,3-hexanediol, the compounds elicited an unexpected complete lack of activity. Subjecting the treated volunteers to conditions inducing sweating (27° and 80% relative humidity) did not improve the activity of the compounds. In view of the reported activity of compounds **1–4**, the lack of activity for compounds **5–7** is indeed surprising. It is apparent that the precursor molecules are not significantly repellent *per se;* moreover, these agents do not hydrolyze at a sufficiently rapid rate to release the minimum effective dose of **8**, and/or the hydrolysis of these silyl ethers does not afford 2-ethyl-1,3-hexanediol as anticipated.

It is interesting to note that insect repellent activity for compounds **1–4** was claimed for the intact molecules; yet it has been shown that volatility is a major factor with regard to insect repellency[15] and, due to the molecular weights of agents **1–7**, they would be expected to have low vapor pressures. Therefore, it is more than likely that the activity of compounds **1–4** is due to their hydrolysis which would

afford 2-ethyl-1,3-hexanediol. If compounds 1–4 were hydrolyzed rapidly enough to release the minimum effective dose of the repellent, then compounds 5–7 might also be expected to hydrolyze at such a rate that *some* repellent activity would be seen unless, of course, the cleavage of these agents did not release diol 8. In the preparation of 18, a compound was obtained which, from spectral data (nmr, ir), was shown to be silanol 22. The isolation of 22 and its



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unexpected stability (as well as that of the corresponding methyl and butyl silanols) suggests that in the instance of 5–7, diol 8 is not a product of hydrolysis—only the corresponding silanols. However, in the instance of compounds 1–4, if hydrolysis to their corresponding silanols occurs, 1 mol of repellent diol 8 would still be released for every mole of compound—hence their activity. However, in the case of compounds 5–7, hydrolysis would not afford a repellent moiety (22 was found devoid of repellent activity). The lack of insectifugal activity of the silyl ether precursor molecules 5–7 is believed to be due to their hydrolysis to the inactive silanols (*e.g.*, 22) (Table I).

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1,6-Bis(N^5-*m*-trifluoromethylphenyl-N^1-biguanido)-hexane and Related Analogs of Chlorhexidine as Inhibitors of Dental Plaque†

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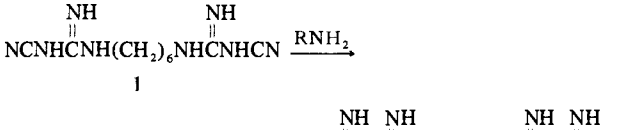
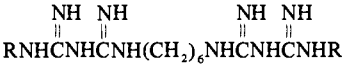
Dental plaque is a soft, tenacious bacterial deposit which forms on the surface of teeth. A close correlation exists between the formation of plaque and the development of caries, gingivitis, and subsequent periodontal disease.[1] Mechan ical cleansing is the principal means of removing plaque and its clinical effectiveness is limited. Since plaque is composed mainly of bacteria, numerous antibacterial agents have been investigated for their ability to inhibit plaque formation and several compounds have been reported to be active.[1-4] Clinical reports[2,3,5] have established that chlorhexidine (2), an antibacterial bisbiguanide, is one of the more effective inhibitors of plaque formation. The toxicity of chlorhexidine is low;[6] however, it does produce minor side effects that preclude general clinical use.[7]

The observation[8] that the phenyl analog 3 of chlorhexidine did not inhibit plaque formation, coupled with the earlier report[6] that variations at this position radically changed antibacterial activity, prompted us to synthesize chlorhexidine analogs 4–6 in an attempt to optimize plaque inhibition.

The synthesis of the analogs was based on the method of Rose and Swain.[9] The general procedure involved treating 1,6-diaminohexane with sodium dicyanamide to give 1,6-bis(N^3-cyano-N^1-guanidino)hexane (1) which on treatment with the appropriate amine gave the desired bisbiguanides.



1



2, R = *p*-ClC_6H_4
3, R = C_6H_5
4, R = cyclohexyl
5, R = 1-adamantyl
6, R = *m*-$CF_3C_6H_4$

Biological Results. Antiplaque activity as displayed by chlorhexidine requires that a compound be an antibacterial agent and therefore the antibacterial activity of the compounds prepared in this work was evaluated *in vitro* against *Streptococcus mutans* No. 6715, a pure strain of plaque forming bacteria.‡ Chlorhexidine (Ayerst Laboratories, Inc.) was tested concurrently.

A solution of the test compound (1 ml) was added to 7.85 ml of trypticase broth, 1 ml of 50% sterile sucrose solution, and 0.15 ml of a 24-hr culture of *S. mutans* No. 6715, and

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‡Isolated at and made available to us by the National Institute of Dental Research.